parameter that is predictive of the ability of each of said oligonucleotide sequences to hybridize to said target nucleotide sequence,

(e) means for storing said parameter values,

(f) means for controlling said computer system to carry out an identification, from said stored parameter values, a subset of oligonucleotide sequences within said number of non-identical oligonucleotide sequences based on an examination of said parameter,

(g) means for storing said subset of oligonucleotide sequences,

(h) means for controlling said computer system to carry out an identification of oligonucleotide sequences in said subset that are in clusters along a region of said nucleotide sequence that is hybridizable to said target nucleotide sequence,

(i) means for storing said oligonucleotide sequences in said subset,

(j) means for controlling said computer system to select, for a cluster, a hybridization oligonucleotide and

B7 Cont'd

(k) means for outputting data relating to said oligonucleotide sequences in said subset.

Please **cancel Claims 41-97** without prejudice to Applicant's filing of divisional applications to the separately patentable subject matter thereof.

REMARKS

Applicant requests reconsideration of their application in view of the foregoing amendments and the discussion that follows. The status of the claims is as follows. Claims 41-97 have been withdrawn from consideration by the Examiner and have been canceled above without prejudice to Applicant's filing of divisional applications to the separately patentable subject matter thereof. With regard to remaining Claims 1-40 and 98-101, Claims 1, 3, 4, 10, 24, 25, 38, 98 and 100 have been amended herein.

Attached hereto is a marked-up version of the changes made to the specification and the claims by the current amendment. The attached pages are captioned "VERSION WITH MARKINGS TO SHOW CHANGES MADE." Although not required, also attached is a clean copy of claims 1-40 and 98-101.

The Amendment

Claim 1 was amended to recite a method for selecting a hybridization oligonucleotide to hybridize to a target nucleotide sequence. Support therefor is in the Specification, for example, original Claim 1. Claim 1 was also amended to recite non-identical in place of unique. Support therefor is in the Specification, for example, page 30, lines 28-29.

Claim 3 was amended to recite non-identical in place of unique. Support therefor is in the Specification, for example, page 30, lines 28-29.

Claim 4 was amended in a manner similar to that in Claim 3.

Claim 10 was amended to recite that the factor is predictive of the ability of an oligonucleotide to hybridize with a target nucleotide sequence. Support therefor is in the Specification, for example, the sentence bridging pages 19 and 20.

Claims 24, 25 and 38 were amended in a manner similar to that in Claim 3.

Claims 98 and 100 were amended in a manner similar to that for Claim 1.

Restriction/Election Requirement

Applicant acknowledges the Examiner's indication that all species elections have been vacated and that all claims in Group I are now under examination.

Obviousness-type Double Patenting

The Examiner provisionally rejected Claims 1-40, 98 and 99 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-40, 97 and 98 of U.S. Patent No. 6,251,588. Applicant is prepared to file a terminal disclaimer upon the Examiner's indication that the claims as amended above satisfy the requirements of 35 U.S.C. 112 and 102.

Rejection under 37 U.S.C. §112

Claims 1-40 and 98-101 were rejected under the second paragraph of the above code section as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicant submits that all of the specific rejections under the above code section have been obviated by the above amendments with the exception of the rejection of Claim 28 and all claims dependent thereon.

Applicant respectfully traverses the rejection of Claim 28 and its dependents under the above code section. The Examiner contends that the phrase "poorly correlated" implies some degree of correlation and requires clearer language. Applicant directs the attention of the Examiner to the Specification, for example, page 26, lines 20-22, where Applicant defines the phrase "poorly correlated." The definition of the phrase in the Specification indicates that, if it is not possible to perform a "good" prediction, as defined via statistics, of one set of numbers from another set of numbers using a simple linear model, then the two sets of numbers are said to be poorly correlated.

Rejection under 37 U.S.C. §102

Claims 1-3, 5-10, 15, 17-22, 98 and 100 were rejected under paragraph (b) of the above code section as being anticipated by Hyndman, *et al.* (Hyndman). Hyndman discloses software to determine optimal oligonucleotide sequences based on hybridization simulation data. The authors indicate that their new computer program, HYBsimulator™ (formerly OligoProbe DesignStation) creates a set of candidate oligonucleotides from a target gene. For each of the candidate oligonucleotides, a large sequence database is searched for sequences that will hybridize to the oligonucleotide. The authors refer to this as computer hybridization simulation (CHS). Using the nearest-neighbor model, the HYBsimulator takes into account mismatches in hybridization and calculates the melting temperature or free energy for hybridization to all sequences in a database. The specificity of each oligonucleotide is then quantified by the number of genes that may hybridize and the predicted melting temperatures or free energies of hybridization to those genes. The CHS data are used to select oligonucleotides based on their specificity with respect to a database.

Hyndman does not anticipate the methods of Claims 1-3, 5-10, 15, 17-22, 98 and 100. Hyndman does not disclose the step of identifying oligonucleotides in a subset of oligonucleotides that are clustered along a region of the nucleotide sequence that is hybridizable to the target nucleotide sequence. The present methods are based on Applicant's discovery that oligonucleotides showing high hybridization efficiencies tend to form clusters. Applicant's claimed methods reflect this discovery in that the claims recite the step of identifying oligonucleotides in the subset that are in clusters along a region of the nucleotide sequence that is

subset of oligonucleotides that are clustered along a region of the nucleotide sequence that is hybridizable to the target nucleotide sequence. The present methods are based on Applicant's discovery that oligonucleotides showing high hybridization efficiencies tend to form clusters. Applicant's claimed methods reflect this discovery in that the claims recite the step of identifying oligonucleotides in the subset that are in clusters along a region of the nucleotide sequence that is hybridizable to the target nucleotide sequence. The Hyndman reference is completely devoid of any teaching in this regard.

As Hyndman explains, HYBsimulator creates a ProbeSet where the set contains all possible oligonucleotides derived for the target sequence that fit a chosen specification (page 1091, column 2, lines 14-17). Designated oligonucleotides are selected from the ProbeSet for a particular application. The specificity of probes in the ProbeSet is determined based on computer hybridization simulation (CHS) data. CHS simulates hybridization of each probe in the ProbeSet with every sequence in a specified GenBank database. HYBsimulator performs multiple calculations for the possible sub-sequences and then selects the most favorable value (paragraph bridging pages 1091 and 1092.

In the present invention a predetermined number of non-identical oligonucleotides within a nucleotide sequence that is hybridizable with the target nucleotide sequence is identified. The oligonucleotides are chosen to sample a length of the nucleotide sequence. For each of the oligonucleotides at least one parameter that is predictive of the ability of each of the oligonucleotides to hybridize to the target nucleotide sequence is determined and evaluated. A subset of oligonucleotides within the predetermined number of non-identical oligonucleotides is selected based on an examination of the parameter. Then, oligonucleotides in the subset are identified that are in clusters along a region of the nucleotide sequence that is hybridizable to the target nucleotide sequence. A hybridization oligonucleotide is selected for each cluster.

CONCLUSION

Claims 1-40 and 98-101 satisfy the requirements of 35 U.S.C. §§112 and 102. Allowance of the above-identified patent application, it is respectfully submitted, is in order. Applicant is prepared to file a terminal disclaimer upon the Examiner's

indication that the claims as amended above satisfy the requirements of 35 U.S.C. 112 and are allowable over the applied reference.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims

The claims have been amended as follows:

1. (**twice amended**) A method for selecting a hybridization oligonucleotide [predicting the potential of an oligonucleotide] to hybridize to a target nucleotide sequence, said method comprising:

(a) identifying a predetermined number of non-identical [unique] oligonucleotides within a nucleotide sequence that is hybridizable with said target nucleotide sequence, said oligonucleotides being chosen to sample a length of said nucleotide sequence,

(b) determining and evaluating for each of said oligonucleotides at least one parameter that is predictive of the ability of each of said oligonucleotides to hybridize to said target nucleotide sequence,

(c) selecting a subset of oligonucleotides within said predetermined number of non-identical [unique] oligonucleotides based on an examination of said parameter,

(d) identifying oligonucleotides in said subset that are in clusters along a region of said nucleotide sequence that is hybridizable to said target nucleotide sequence and

(e) selecting, for a cluster, a hybridization oligonucleotide.

3. (**amended**) A method according to Claim 1 wherein said non-identical [unique] oligonucleotides are of identical length N.

4. (**amended**) A method according to Claim 3 wherein said non-identical [unique] oligonucleotides are spaced one nucleotide apart, said predetermined number comprising L-N+1 oligonucleotides, where L is the length of the hybridizable sequence.

10. (**amended**) A method according to Claim 1 wherein said parameter is derived from a factor by mathematical transformation of said factor wherein said factor is predictive of the ability of an oligonucleotide to hybridize with a target nucleotide sequence.

24. (**amended**) A method according to Claim 1 wherein step (c) comprises identifying a subset of oligonucleotides within said predetermined number of non-identical [unique] oligonucleotides by establishing cut-off values for said parameter.

25. (**amended**) A method according to Claim 1 wherein said step (c) comprises identifying a subset of oligonucleotides within said predetermined number of non-identical [unique] oligonucleotides by converting the values of said parameter into a dimensionless number.

38. (**amended**) A method according to Claim 1 which comprises (i) identifying a subset of oligonucleotides within said predetermined number of non-identical [unique] oligonucleotides by establishing cut-off values for each of said parameters.

98. (**twice amended**) A computer based method for selecting a hybridization oligonucleotide [predicting the potential of an oligonucleotide] to hybridize to a target nucleotide sequence, said method comprising:

(a) identifying under computer control a predetermined number of non-identical [unique] oligonucleotides within a nucleotide sequence that is hybridizable with said target nucleotide sequence, said oligonucleotides being chosen to sample a length of said nucleotide sequence,

(b) under computer control, determining and evaluating for each of said oligonucleotides a value for at least one parameter that is predictive of the ability of each of said oligonucleotides to hybridize to said target nucleotide sequence and storing said parameter values,

(c) selecting under computer control, from said stored parameter values, a subset of oligonucleotides within said predetermined number of non-identical [unique] oligonucleotides based on an examination of said parameter,

(d) identifying under computer control oligonucleotides in said subset that are in clusters along a region of said nucleotide sequence that is hybridizable to said target nucleotide sequence and

(e) under computer control selecting, for a cluster, a hybridization oligonucleotide.

100. (**twice amended**) A computer system for conducting a method for selecting a hybridization oligonucleotide [predicting the potential of an oligonucleotide] to hybridize to a target nucleotide sequence, said method comprising:

(a) input means for introducing a target nucleotide sequence into said computer system,

(b) means for determining a number of non-identical [unique] oligonucleotides that are within a nucleotide sequence that is hybridizable with said target nucleotide sequence, said oligonucleotide sequences being chosen to sample a length of said nucleotide sequence,

(c) memory means for storing said oligonucleotide sequences,

(d) means or controlling said computer system to carry out a determination and evaluation for each of said oligonucleotide sequences a value for at least one parameter that is predictive of the ability of each of said oligonucleotide sequences to hybridize to said target nucleotide sequence,

(e) means for storing said parameter values,

(f) means for controlling said computer system to carry out an identification, from said stored parameter values, a subset of oligonucleotide sequences within said number of non-identical [unique] oligonucleotide sequences based on an examination of said parameter,

(g) means for storing said subset of oligonucleotide sequences,

(h) means for controlling said computer system to carry out an identification of oligonucleotide sequences in said subset that are in clusters along a region of said nucleotide sequence that is hybridizable to said target nucleotide sequence,

(i) means for storing said oligonucleotide sequences in said subset,

(j) means for controlling said computer system to select, for a cluster, a hybridization oligonucleotide and

(k) means for outputting data relating to said oligonucleotide sequences in said subset.

Claims 41-97 were canceled without prejudice to Applicant's filing of divisional applications to the separately patentable subject matter thereof.

CLEAN COPY OF CLAIMS 1-40 AND 98-101

1. (**twice amended**) A method for selecting a hybridization oligonucleotide to hybridize to a target nucleotide sequence, said method comprising:

(a) identifying a predetermined number of non-identical oligonucleotides within a nucleotide sequence that is hybridizable with said target nucleotide sequence, said oligonucleotides being chosen to sample a length of said nucleotide sequence,

(b) determining and evaluating for each of said oligonucleotides at least one parameter that is predictive of the ability of each of said oligonucleotides to hybridize to said target nucleotide sequence,

(c) selecting a subset of oligonucleotides within said predetermined number of non-identical oligonucleotides based on an examination of said parameter,

(d) identifying oligonucleotides in said subset that are in clusters along a region of said nucleotide sequence that is hybridizable to said target nucleotide sequence and

(e) selecting, for a cluster, a hybridization oligonucleotide.

2. A method according to Claim 1 which comprises ranking said oligonucleotides of step (d) based on the size of said clusters of oligonucleotides.

3. (**amended**) A method according to Claim 1 wherein said non-identical oligonucleotides are of identical length N.

4. (**amended**) A method according to Claim 3 wherein said non-identical oligonucleotides are spaced one nucleotide apart, said predetermined number comprising L-N+1 oligonucleotides, where L is the length of the hybridizable sequence.

5. A method according to Claim 1 wherein said parameter is selected from the group consisting of composition factors, thermodynamic factors, chemosynthetic efficiencies and kinetic factors.

6. A method according to Claim 1 wherein said parameter is a composition factor selected from the group consisting of mole fraction (G+C), percent (G+C), sequence complexity, and sequence information content.

7. A method according to Claim 1 wherein said parameter is a thermodynamic factor selected from the group consisting of predicted duplex melting temperature, predicted enthalpy of duplex formation, predicted entropy of duplex formation, predicted free energy of duplex formation, predicted melting temperature of the most stable intramolecular structure of the oligonucleotide or its complement, predicted enthalpy of the most stable intramolecular structure of the oligonucleotide or its complement, predicted entropy of the most stable intramolecular structure of the oligonucleotide or its complement, predicted free energy of the most stable intramolecular structure of the oligonucleotide or its complement, predicted melting temperature of the most stable hairpin structure of the oligonucleotide or its complement, predicted enthalpy of the most stable hairpin structure of the oligonucleotide or its complement, predicted entropy of the most stable hairpin structure of the oligonucleotide or its complement, predicted free energy of the most stable hairpin structure of the oligonucleotide or its complement, thermodynamic partition function for intramolecular structure of the oligonucleotide or its complement.

8. A method according to Claim 1 wherein said parameter is a chemosynthetic efficiency selected from the group consisting of coupling efficiencies and overall efficiency of the synthesis of a target nucleotide sequence or an oligonucleotide probe.

9. A method according to Claim 1 wherein said parameter is a kinetic factor selected from the group consisting of steric factors calculated via molecular modeling, rate constants calculated via molecular dynamics simulations, rate constants calculated via semi-empirical kinetic modeling, associative rate constants, dissociative rate constants, enthalpies of activation, entropies of activation, and free energies of activation.

10. (**amended**) A method according to Claim 1 wherein said parameter is derived from a factor by mathematical transformation of said factor wherein said factor is predictive of the ability of an oligonucleotide to hybridize with a target nucleotide sequence.

11. A method according to Claim 1 which comprises ranking said clustered oligonucleotides of step (d) based on the size of said clusters of oligonucleotides and selecting a subset of said clustered oligonucleotides.

12. A method according to Claim 11 wherein said subset consists of any number of oligonucleotides within said cluster of oligonucleotides.

13. A method according to Claim 11 wherein the subset of said clustered oligonucleotides are selected to statistically sample the cluster.

14. A method according to Claim 13 wherein said statistical sample consists of oligonucleotides spaced at the first quartile, median and third quartile of the cluster of oligonucleotides.

15. A method according to Claim 1 wherein said parameters are determined for said oligonucleotides by means of a computer program.

16. A method according to Claim 1 wherein said oligonucleotides are attached to a surface.

17. A method according to Claim 1 wherein said oligonucleotides are DNA.

18. A method according to Claim 1 wherein said oligonucleotides are RNA.

19. A method according to Claim 1 wherein said oligonucleotides contain chemically modified nucleotides.

20. A method according to Claim 1 wherein said target nucleotide sequence is RNA.

21. A method according to Claim 1 wherein said target nucleotide sequence is DNA.

22. A method according to Claim 1 wherein said target nucleotide sequence contains chemically modified nucleotides.

23. A method according to Claim 1 wherein said parameter is, for each oligonucleotide/target nucleotide sequence duplex, the difference between the predicted

duplex melting temperature corrected for salt concentration and the temperature of hybridization of each of said oligonucleotides with said target nucleotide sequence.

24. (**amended**) A method according to Claim 1 wherein step (c) comprises identifying a subset of oligonucleotides within said predetermined number of non-identical oligonucleotides by establishing cut-off values for said parameter.

25. (**amended**) A method according to Claim 1 wherein said step (c) comprises identifying a subset of oligonucleotides within said predetermined number of non-identical oligonucleotides by converting the values of said parameter into a dimensionless number.

26. A method according to Claim 25 wherein said value is converted into a dimensionless number by determining a dimensionless score for each parameter resulting in a distribution of scores having a mean value of zero and a standard deviation of one.

27. A method according to Claim 26 which comprises optimizing a method according to calculation for said parameter based on said individual scores.

28. A method according to Claim 1 wherein step (b) comprises determining at least two parameters wherein said parameters are poorly correlated with respect to one another.

29. A method according to Claim 28 wherein said parameters are derived from a combination of factors by mathematical transformation of those factors.

30. A method according to Claim 1 wherein step (b) comprises determining two parameters at least one of said parameters being the association free energy between a subsequence within each of said oligonucleotides and its complementary sequence on said target nucleotide sequence.

31. A method according to Claim 30 wherein said subsequence is 3 to 9 nucleotides in length.

32. A method according to Claim 30 wherein said subsequence is 5 to 7 nucleotides in length.

33. A method according to Claim 30 wherein said subsequence is at least three nucleotides from the terminus of said oligonucleotides.

34. A method according to Claim 30 wherein said subsequence is at least three nucleotides from a surface to which said oligonucleotides are attached.

35. A method according to Claim 30 wherein said oligonucleotides are attached to a surface and said subsequence is at least five nucleotides from the terminus of said oligonucleotides that is attached to said surface and at least three nucleotides from the free end of said oligonucleotides.

36. A method according to Claim 30 wherein the association free energy of the members of a set of subsequences within each of said oligonucleotides is determined and said subsequence having the minimum value is identified.

37. A method according to Claim 1 which comprises including oligonucleotides that are adjacent to said oligonucleotides in said subset that are clustered along a region of said target nucleotide sequence.

38. (**amended**) A method according to Claim 1 which comprises (i) identifying a subset of oligonucleotides within said predetermined number of non-identical oligonucleotides by establishing cut-off values for each of said parameters.

39. A method according to Claim 1 which comprises determining the sizes of said clusters of step (d) by counting the number of contiguous oligonucleotides in said region of said hybridizable sequence.

40. A method according to Claim 1 which comprises determining the sizes of said clusters of step (d) by counting the number of oligonucleotides in said subset that begin in a region of predetermined length in said hybridizable sequence.

98. **(twice amended)** A computer based method for selecting a hybridization oligonucleotide to hybridize to a target nucleotide sequence, said method comprising:

(a) identifying under computer control a predetermined number of non-identical oligonucleotides within a nucleotide sequence that is hybridizable with said target nucleotide sequence, said oligonucleotides being chosen to sample a length of said nucleotide sequence,

(b) under computer control, determining and evaluating for each of said oligonucleotides a value for at least one parameter that is predictive of the ability of each of said oligonucleotides to hybridize to said target nucleotide sequence and storing said parameter values,

(c) selecting under computer control, from said stored parameter values, a subset of oligonucleotides within said predetermined number of non-identical oligonucleotides based on an examination of said parameter,

(d) identifying under computer control oligonucleotides in said subset that are in clusters along a region of said nucleotide sequence that is hybridizable to said target nucleotide sequence and

(e) under computer control selecting, for a cluster, a hybridization oligonucleotide.

99. A method according to claim 98 wherein the identified subset of oligonucleotide sequences is electronically transferred to an oligonucleotide array manufacturing system.

100. **(twice amended)** A computer system for conducting a method for selecting a hybridization oligonucleotide to hybridize to a target nucleotide sequence, said method comprising:

(a) input means for introducing a target nucleotide sequence into said computer system,

(b) means for determining a number of non-identical oligonucleotides that are within a nucleotide sequence that is hybridizable with said target nucleotide sequence, said oligonucleotide sequences being chosen to sample a length of said nucleotide sequence,

(c) memory means for storing said oligonucleotide sequences,

(d) means or controlling said computer system to carry out a determination and evaluation for each of said oligonucleotide sequences a value for at least one parameter that is predictive of the ability of each of said oligonucleotide sequences to hybridize to said target nucleotide sequence,

(e) means for storing said parameter values,

(f) means for controlling said computer system to carry out an identification, from said stored parameter values, a subset of oligonucleotide sequences within said number of non-identical oligonucleotide sequences based on an examination of said parameter,

(g) means for storing said subset of oligonucleotide sequences,

(h) means for controlling said computer system to carry out an identification of oligonucleotide sequences in said subset that are in clusters along a region of said nucleotide sequence that is hybridizable to said target nucleotide sequence,

(i) means for storing said oligonucleotide sequences in said subset,

(j) means for controlling said computer system to select, for a cluster, a hybridization oligonucleotide and

(k) means for outputting data relating to said oligonucleotide sequences in said subset.

101. A computer system according to claim 100 wherein the identified subset of oligonucleotide sequences is electronically transferred to an oligonucleotide array manufacturing system.